Pregabalin Population Pharmacokinetic and Exposure-Response Analyses for Focal Onset Seizures in Children (4–16 years) and Adults, to Support Dose Recommendations in Children

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Pregabalin is approved in multiple countries as adjunctive therapy for adult patients with focal onset seizures (FOS; previously termed partial onset seizures). This study used population pharmacokinetic (PK) and exposure–response (E-R) analyses from pooled pregabalin concentration and efficacy data to compare pregabalin exposure and E-R relationships in pediatric and adult patients with FOS, to support pediatric dosage recommendations. A one-compartment disposition model was used, with first-order absorption and body surface area-normalized creatinine clearance on clearance. Individual pregabalin average steady-state concentrations were predicted and used in an E-R analysis of efficacy. The E-R relationship of pregabalin was similar in pediatric (4–16 years) and adult patients with FOS after accounting for differences in baseline natural log-transformed 28-day seizure rate and placebo effect. Population PK simulations showed that children aged 4–16 years and weighing ≥ 30 kg required pregabalin 2.5–10 mg/kg/day to achieve similar pregabalin exposure at steady-state to adult patients receiving the approved doses of 150–600 mg/day. For children 4–16 years weighing < 30 kg, a higher pregabalin dose of 3.5–14 mg/kg/day was required to achieve equivalent exposure at steady-state. The results support the dosage guidance provided in the pregabalin prescribing label, whereby pediatric patients (4–16 years) weighing < 30 kg should receive a 40% higher pregabalin dose (per kg of body weight) than patients weighing ≥ 30 kg to achieve similar exposure. Our combined modeling approach may provide guidance for future extrapolation assessment from adult to pediatric patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Full extrapolation of the efficacy of drugs approved for the treatment of focal onset seizures in adults, to children 2 years of age and older, is accepted by the US Food and Drug Administration (FDA).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Population pharmacokinetics (PK) in adults and children, and subsequent exposure–response (E-R) analyses confirmed drug exposure and E-R relationship similarities in the two populations with focal onset seizures, and supported pregabalin pediatric dosage recommendations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The similarities in PK exposure and E-R relationship of pregabalin in adult and pediatric patients served as further validation of the established full extrapolation in focal onset seizures.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Applying the extrapolation, modeling and simulation approach may facilitate more efficient pediatric drug development and approval, and more timely access to new treatments for pediatric patients.

Pregabalin (LYRICA) is a second-generation antiepileptic drug (AED) approved as adjunctive therapy (either b.i.d. or t.i.d. daily-dosing) for adults with focal onset seizures (FOS; previously termed partial onset seizures[1]), in addition to being approved for other indications, including neuropathic pain.[2,3] In the United States, pregabalin is also approved as adjunctive therapy for FOS in pediatric patients aged 1 month and older.[2] Approval in pediatric patients with FOS occurred after completion of pediatric phase I, phase III safety and efficacy, and long-term safety trials,[4] and 15 years after approval for adults with FOS.[2] In adults with FOS, adjunctive flexible-dosed pregabalin (150–600 mg/day) reduces seizure frequency and increases responder rates (i.e., proportion of patients achieving ≥ 50% reduction in seizure frequency) vs. placebo.[5–7]

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Pregabalin has a linear and predictable pharmacokinetic (PK) profile.[8,9] In adults, pregabalin is well absorbed after oral administration with time to peak plasma concentrations (T_{max}) within 1.5 hours postdose under fasting conditions, and oral bioavailability is ≥ 90% independent of dose. Pregabalin does not bind to plasma proteins. The apparent volume of distribution (V/F) following oral administration is ~ 0.5 L/kg. Pregabalin undergoes negligible metabolism in humans, and is largely eliminated by renal excretion, with elimination half-life of ~ 6 hours.[2]

Population PK analyses in adults have shown that creatinine clearance (CLcr) is a significant covariate predicting apparent clearance (CL/F).[8,9] Although a small additional relationship with body weight has been detected,[9] the relationship with CLcr (mL/min) accounts for most of the changes in CL/F due to both size and renal function, and is the only clinically relevant covariate in adults.[8] In a phase I study, including pediatric patients aged 1 month to 16 years, the observed pregabalin T_{max} was similar to that observed in adults.[10] However, body weight–normalized pregabalin CL/F was ~ 40% higher in patients weighing < 30 kg vs. those weighing ≥ 30 kg, consistent with the lower area under the concentration–time curve (AUC) observed in younger children when pregabalin is administered on a mg/kg basis.[10] Body weight is also a factor on V/F, but when normalized for body weight, V/F was similar across age cohorts and body weight.[10] As a result, mean terminal half-life of pregabalin was lower in patients weighing < 30 kg, consistent with the higher body weight-normalized CL/F in patients 1 month to 6 years and the constant body weight-normalized V/F across age cohorts, as reported in full elsewhere.[10] A 40% higher pregabalin dose (in mg/kg) is safe and effective for pediatric patients weighing < 30 kg, to achieve similar PK exposures to adults, or to pediatric patients weighing ≥ 30 kg.[10] These extrapolations were subsequently used in the design of the phase III PERIWINKLE study in pediatric patients (4–16 years) with FOS (NCT01389596; A0081041), where two dose groups of adjunctive pregabalin (2.5 mg/kg/day (max 150 mg/day); 10 mg/kg/day (max 600 mg/day)) were investigated. Doses were adjusted to 3.5 and 14 mg/kg/day, respectively, for children weighing < 30 kg to match corresponding exposures in adults.[4] PERIWINKLE demonstrated that pregabalin (10 mg/kg/day) significantly reduced FOS frequency vs. placebo.[4] The lower dose (pregabalin 2.5 mg/kg/day) showed a numerical, but nonsignificant reduction in FOS frequency vs. placebo.[4] The US Food and Drug Administration (FDA) has since issued guidance indicating that efficacy of treatments in adults with FOS can be extrapolated to pediatric patients aged ≥ 2 years.[11,12] We sought to use population PK and exposure–response (E-R) analyses to compare pregabalin exposure and E-R relationships in pediatric and adult patients with FOS. These analyses informed dosage guidance in the pregabalin prescribing label.[2,11]

METHODS

Overall strategy

Population PK modeling was performed using pooled pregabalin concentration data in pediatric and adult patients, and an adapted version of a previously developed population PK model based on adult data.[9] Predicted individual pregabalin average steady-state concentrations ($C_{av,ss}$) in pediatric and adult efficacy studies were subsequently used in the pooled E-R efficacy analysis. Based on pregabalin E-R similarity in pediatric and adult patients with FOS, population PK simulations were performed to assess the proposed dosing recommendations for pediatric patients 4–16 years, aiming for children to achieve similar pregabalin concentrations to approved doses in adults with FOS.

Population PK model

Pregabalin plasma concentrations from healthy participants with various degrees of renal function and from patients with FOS across 10 studies were included in the population PK dataset. These included two studies in pediatric patients with FOS,[4,10] three phase III studies in adult patients with FOS,[5–7] four phase I studies in healthy adults,[9,13,14] and one study in adults with various degrees of renal function.[15] All studies were approved by relevant institutional review boards, as detailed elsewhere.[4–7,9,10,13–15]

The population PK model was built using nonlinear mixed-effects modeling (NONMEM), first-order conditional estimation with interaction and NONMEM software version 7.3 (Icon Development Solutions, Dublin, Ireland). The base model was a one-compartment model with first-order elimination and absorption (first-order absorption rate constant (k_a), which was modeled as a fraction of the elimination rate constant to avoid flip-flop), with lag time (T_{lag}).[9] Previously identified structural covariates included the effect of CLcr on pregabalin CL/F, using a breakpoint model, the effects of body weight and sex on pregabalin V/F, and food effect on k_a.[9] A breakpoint is necessary in populations where CLcr estimates using Cockcroft-Gault equation may be overestimated for overweight subjects.[16] For all subjects ≥ 13 years, CLcr was calculated with the Cockcroft-Gault equation, using serum creatinine, age, body weight, and sex, in line with the approved pregabalin labeling.[2,3] For pediatric subjects (1–12 years), CLcr was estimated by the modified Schwartz equation in mL/min/1.73 m^2, with $K = 0.55$ and corrected for individual baseline body surface area (BSA) in mL/min (non-normalized). For pediatric subjects < 1 year, $K = 0.45$ was used.

While retaining all previous covariate effects, the relationship between pregabalin CL/F and body weight was adapted to use BSA–normalized CLcr (NCLcr) prior to assessing other covariate effects. Interindividual variability (IIV) of PK parameters (CL/F, V/F, k_a, and T_{lag}) were modeled using multiplicative exponential random effects. Residual variability was modeled as additive and proportional in the linear domain. The influence of additional demographics (age, sex, and race) on CL/F and V/F was examined using a stepwise forward selection and backward elimination approach, with significance level of $\alpha = 0.001$ (change in objective function value = 10.83). The body weight effects on CL/F and V/F were estimated using power functions normalized to 70 kg with estimated exponents. Equations used to model covariate relationships are shown in the **Appendix File**. Predictive performance of the final population PK model was evaluated by prediction-corrected visual predictive checks with stratification by age group.[17]

Exposure–response model

The E-R relationship between predicted individual pregabalin $C_{av,ss}$ generated by the final population PK model and natural log-transformed 28-day seizure rate (LSR28) was evaluated by nonlinear least-squares regression. Efficacy data from pediatric patients with FOS (4–16 years[4]) were combined with three adult studies,[5–7] including eight adolescents with FOS.[7] A set of models covering no drug effect, linear effect, and maximum response achievable (E_{max}) were used to describe the E-R relationship between $C_{av,ss}$ and LSR28 during the 12-week double-blind treatment phase (**Appendix File**). The impact of baseline LSR28 and the need for separate placebo response or efficacy parameters (e.g., slope for linear model and E_{max} or half maximal-effective concentration (EC_{50}) of pregabalin for E_{max} model) were used

to test for differences in E-R between pediatric and adult populations. **Figure 1** graphically illustrates the drug effect vs. placebo response in pediatric and adult populations, showing the common E_{max} and EC_{50} parameters but different placebo responses, based on individuals' baseline LSR28. Model selection was based on Akaike Information Criterion, model stability, plausibility, and precision (standard error of parameter estimates and residual error). Adult data were used initially to develop the structural model, and pediatric data were added to test for population differences. A graphical analysis was used to assess adequacy of the final regression model in describing the E-R relationship for subgroups of covariates of interest (age, sex, race, geographic region, and number concomitant AEDs).

Pediatric dosage recommendations

In order to evaluate the pediatric dosage recommendations, simulation data sets (n = 1,000) with appropriate covariates were created by bootstrapping with replacement from 331 pediatric patients with FOS (4–16 years) in the two pediatric studies (including placebo arms), and by sampling without replacement from 1,040 adult patients with FOS in the three phase III studies. Population PK simulations were performed under fasted conditions, with final parameter estimates, all covariate effects, IIV, and residual errors from the final population PK model for 150 and 600 mg/day equivalent adult doses. The simulated steady-state pregabalin concentrations ($C_{av,ss}$, maximum ($C_{max,ss}$), minimum ($C_{min,ss}$)) for pediatric and adult patients were compared. Dosage recommendations for children aged 4–16 years were determined based on matching adult exposures at approved dosages per the FDA's guidance on full extrapolation of efficacy from adults to pediatric patients with FOS.[11,12] Although only the b.i.d. regimen was investigated in PERIWINKLE, both b.i.d. and t.i.d. regimens were simulated in pediatric patients, as both regimens are approved in adult patients.[2,3]

RESULTS

Population PK model

Serum concentrations were included for PK analysis from 724 adults and 255 pediatric patients across the 10 pregabalin studies. The majority of patients were white in each age category, with approximately equal proportions of male and female patients (**Table 1**). CLcr ranged between 42.2 and 261 mL/min in adults, and between 15.5 and 293 mL/min in pediatric patients. A total of 45 of 162 patients aged < 12 years had absolute CLcr < 60 mL/min. After adjusting for body size (based on BSA), BSA-NCLcr was comparable in pediatric patients aged < 12 years and those ≥ 12 years (**Table 1**).

Based on highly correlated covariates of absolute CLcr, body weight, and age, particularly in the pediatric population, the BSA-NCLcr one-compartment model (including allometric scaling of body weight on pregabalin CL/F and V/F with estimated exponents) was chosen as the final model as it was more stable than the model with absolute CLcr (**Table 2**). Although the initial approach is still valid, the BSA-NCLcr (mL/min/1.73 m^2) approach was used to reduce colinearities among covariates and stabilize model building. IIV on T_{lag} was fixed to 0 due to limited number of observations prior to the estimated T_{lag} (~ 0.32 hours). The goodness-of-fit plots and the prediction-corrected visual predictive check, stratified by study design variables and covariates, indicated that the final combined pediatric and adult population PK model adequately described the pregabalin PK in pediatric patients with FOS, healthy adults, adults with various degrees of renal function, and adults with FOS (**Figure S1**; **Figure S2**). The two nominal dose levels, 2.5 and 10 mg/kg/day, were observed to deliver similar concentrations to the adult doses, 150 and 600 mg/day, respectively (**Figure S3**) as predicted from prior modeling, including phase I pediatric data.[18] The estimated exponent of allometric function was 0.52 for CL/F and 0.70 for V/F. This translates to ~ 40% higher CL/F for a typical child weighing 20 kg compared with a typical child weighing 40 kg. In addition to the previously identified covariate effects (food effect on k_a and T_{lag}, body weight and sex on V/F), a statistically significant sex effect on CL/F was observed, but the 8% lower CL/F in female patients was not considered clinically relevant (**Table S1**). Inclusion of food effect on T_{lag} and sex on CL/F only slightly reduced IIV on CL (from 20.8% to 20.2%), V/F (from 13.0% to 12.8%), and $k_{a,fed}$ (from 59.2% to 57.9%), whereas IIV on k_a remained unchanged (117%).

Exposure–response model

The E-R model was developed based on data from 280 pediatric patients (4–16 years) in the PERIWINKLE study and 858 adult patients (including 8 adolescents 13–16 years) in the 3 adult studies with FOS (**Table S2**). There was an approximately equal proportion of male and female patients among the adult and pediatric populations. Most patients were white (82%) and from the United States (62%); 29% of pediatric patients were Asian vs. 1% of adult

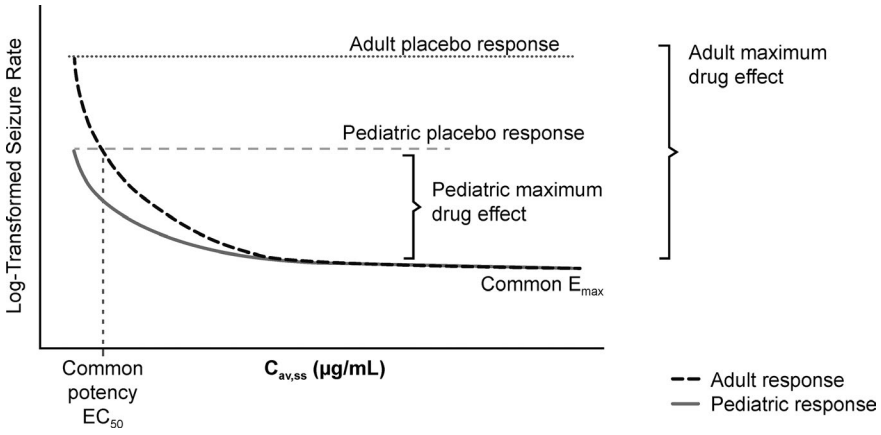

Figure 1 Graphical representation of exposure–response (E-R) in children and adult patients with FOS. $C_{av,ss}$, average steady-state concentration; EC_{50}, half maximal effective concentration; E_{max}, maximum response achievable; FOS, focal onset seizures.

Table 1 Demographic characteristics of patients included in the population PK analysis

	Children (3 months to 16 years)			
	3 months to < 12 years	12–16 years	All	Adults
N	162	93	255	724
Females, *n* (%)	80 (49.4)	41 (44.1)	121 (47.5)	367 (50.7)
Age, years, median (range)	7 (0.25–11)	14 (12–16)	10 (0.25–16)	38 (17–75)
Race, *n* (%)				
White	112 (69)	65 (70)	177 (69)	608 (84)
Black	11 (7)	2 (2)	13 (5)	38 (5)
Asian	34 (21)	23 (25)	57 (22)	11 (2)
Others	5 (3)	3 (3)	8 (3)	67 (9)
Body weight, kg, median (range)	23.6 (6.6–69)	52.3 (24–108)	32.9 (6.6–108)	75.5 (40–180)
CLcr, mL/min, median (range)	79.1 (15.5–193)	128 (67.2–293)	95.5 (15.5–293)	108[a] (42.2–261) 46.5[b] (10.0–122)
NCLcr, mL/min/1.73 m^2, median (range)	149 (74–315)	149 (94–284)	149 (74–315)	101[a] (49–227) 42[b] (9.94–117)
Total no. PK samples	628	313	941	4,317

CLcr, creatinine clearance; NCLcr, creatinine clearance estimated using Cockcroft-Gault equation (normalized for body surface area) for patients ≥ 13 years and Schwartz equation for patients < 13 years; PK, pharmacokinetic.
[a]Excluded 26 patients with renal dysfunction from a phase I study.[10] [b]Patients in protocol 1008-049 included adults with various degrees of renal function, including normal renal function.

patients. The proportions of patients on one or two concomitant AEDs were comparable between pediatric and adult patients. None of the pediatric patients were on ≥ 4 concomitant AEDs (**Table S2**).

The relationship between pregabalin $C_{av,ss}$ and LSR28 in pediatric patients aged 4–16 years and adult patients with FOS was best described with a model based on a common E_{max} (sum of population-specific placebo effect and maximum drug effect), a common EC_{50}, and separate baseline LSR28 and placebo effects for the two populations (**Figure 1**). There was a trend for dose-response relationship despite the large between-subject variability in both pediatric and adult patients (**Figure 2**). The mean change from baseline for 600 mg/day b.i.d in adults and the highest dose (10 mg/kg/day) in pediatric patients were similar (−0.545 vs. −0.551). The group means (−0.313 vs. −0.0296) and medians (−0.185 vs. −0.0150) of change from baseline in LSR28 for pediatric patients on placebo were higher than adults on placebo, respectively. The E-R relationship of pregabalin was similar across pediatric patients aged 4–16 years and adult patients with FOS, after accounting for differences in baseline LSR28 and placebo effect in the 2 populations (**Table 3**; **Figure S4**). When assessed graphically, none of the covariates appeared influential on the E-R relationship of LSR28 and pregabalin $C_{av,ss}$ for pediatric and adult patients, including age or sex (**Figures S5a,b**).

Projected dosage recommendations in children

Population PK simulations demonstrated that in pediatric patients aged 4–16 years, weighing ≥ 30 kg, a pregabalin dose of 2.5–10 mg/kg/day given either b.i.d. or t.i.d. achieved similar pregabalin exposure to adult patients receiving 150–600 mg/day (the approved dose in adults[2,3]). For pediatric patients 4–16 years, weighing < 30 kg, a 40% higher pregabalin dose (3.5–14 mg/kg/day) was required to achieve this exposure given either b.i.d. or t.i.d. (**Table 4**; **Table S3**).

DISCUSSION

The pregabalin pediatric FOS program was started in 2005, prior to regulatory guidelines on Paediatric Investigational Plans (PIP),[19] Pediatric Study Plans (PSP),[11] and the acceptance of efficacy extrapolation by the FDA from adult to pediatric patients with FOS.[11,12] The program included a phase I PK study in pediatric patients with FOS (1 month to 16 years),[10] and two randomized, double-blind, placebo-controlled efficacy and safety studies in pediatric patients with FOS, aged 4–16 years (PERIWINKLE)[4] or 1 month to < 4 years,[20] in addition to long-term safety and tolerability assessments. Shortly before completion of PERIWINKLE in 2016, the FDA announced that efficacy data could be extrapolated from adults to represent pediatric patients with FOS,[21] in order to improve pediatric drug development efficiency and early access to therapeutics. The confirmation of efficacy extrapolation took > 2 decades of multidisciplinary collaboration among multiple sectors from the initial extrapolation proposal,[22,23] to the consensus of disease similarity,[24] to confirmation of efficacy response similarity,[25] and drug E-R similarity across multiple drugs in multiple mechanisms of actions.[11,21] Collectively, guidances were issued

Table 2 Final population PK model (NCLcr) parameter estimates

	Model	Estimate [RSE]	95% confidence interval[a]	Shrinkage
	OFV (ΔOFV[b])	–2803.456 (–227.23)		
Model parameter	CL/F[c]	4.96 [1.78] L/hr	(4.71–5.20)	
	Body weight on CL/F[d]	0.52 [4.72]	(0.48–0.57)	
	Sex on CL/F[e]	0.92 [2.00]	(0.88–0.95)	
	CLcr breakpoint	96.4 [1.91] mL/min/1.73 m^2	(90.7–104)	
	V/F	39.8 [1.62] L	(38.6–41.0)	
	Sex on V/F[e]	0.83 [2.48]	(0.79–0.87)	
	Body weight on V/F[d]	0.70 [4.59]	(0.64–0.76)	
	k_a fasted[f]	10.0 [16.2]/hr	(7.44–15.1)	
	Food: fed[g]	0.71 [2.39]	(0.33–5.14)	
	Food: unknown[g]	1.22 [3.26]	(0.49–3.57)	
	T_{lag}	0.32 [1.52] hr	(0.31–0.32)	
	Food: fed[h]	0.43 [10.5]	(0.34–0.83)	
Interindividual variability	CL/F	20.2 [18.7]%	(16.3–23.4)	27.4%
	V/F	12.8 [21.7]%	(10.3–15.3)	60.7%
	k_a	117 [13.9]%	(103–149)	46.2%
	k_a: fed	57.9 [74.4]%	(25.5–204)	89.6%
Proportional error	Phase I adult	16.6 [10.1]%	(15.2–18.6)	8.2%
	Phase III adult	28.9 [7.49]%	(26.6–30.8)	13.5%
	Phase I pediatric	29.8 [22.7]%	(23.2–36.2)	11.4%
	Phase III pediatric	35.0 [21.0]%	(28.1–40.3)	10.3%
Additive error	Phase I adult	0.021 [66.8] μg/mL	(0.0074–0.033)	5.15%
	Phase III adult	0.047 [77.3] μg/mL	(0.00047–0.092)	13.5%
	Phase III pediatric	0.68 [67.6] μg/mL	(0.0066–1.04)	10.3%

CLcr, creatinine clearance; CL/F, apparent clearance; k_a, absorption rate constant; NCLcr, creatinine clearance (normalized for body surface area); OFV, objective function value; ΔOFV, difference in OFV; PK, pharmacokinetics; RSE, relative standard error; T_{lag}, lag time; V/F, volume of distribution.
[a]95% confidence intervals were generated from 1,000 nonparametric bootstrap data sets. [b]Comparison with the base body-surface area-normalized CLcr model. [c]CL/F estimated as a proportionality factor for the relationship between CL/F and CLcr when CLcr ≤ CLcr breakpoint. [d]Normalized to 70 kg with a power function. [e]Reference sex is male. [f]k_a estimated as a proportionality factor for the relationship between k_a and elimination rate constant. [g]Estimated as a fractional change in k_a. [h]Fractional change in T_{lag} using fed data from a phase I adult study. All phase III adult studies were collected under unknown food status.[5–7] The food status in study A0081041[4] was a diary end point that did not provide information on quantity of type of food consumed. Covariate equations are detailed in the **Appendix, Equations I**.

by the FDA in an attempt to limit the need for a full, controlled clinical efficacy trials in young patients,[11,12] and these are based on the assumptions that, compared with adults, even young children have a similar progression of disease, similar response of disease to treatment, and similar E-R relationship.[11,12]

Using data pooled from 10 adult and pediatric clinical studies of pregabalin, we first demonstrate that in pediatric and adult patients with FOS, pregabalin CL/F was proportional to absolute CLcr (mL/min). However, the high correlations among absolute CLcr, body weight, and age, particularly in the pediatric population, made it difficult to assess these covariate effects independently. The final BSA-NCLcr model, including scaling of body weight on pregabalin CL/F and V/F with estimated exponents, was more stable than the model using the absolute CLcr. Model instability was judged by difficulties in minimization and large changes (> 20%) in parameter estimates. When BSA-NCLcr (mL/min/1.73 m^2) was used to remove colinearities among the covariates, the change in CL/F with size in pediatric patients was accounted for by a relationship with body weight. Pregabalin clearance was proportional to BSA-NCLcr up to an estimated breakpoint of 96.4 mL/min/1.73 m^2, where it was then estimated to be constant for higher BSA-NCLcr. We also noted that most pediatric patients had normal renal function with BSA-NCLcr close to or above the estimated breakpoint.

The IIVs for pregabalin CL/F and V/F were ≤ 20% and the proportional residual errors were ≤ 35%, suggesting pregabalin exposures ($C_{av,ss}$ and $C_{max,ss}$) are highly predictable in both adult and pediatric patients with known body weight and BSA-NCLcr. There was a high ETA-shrinkage for V/F (60.7%), potentially due to limited pregabalin concentrations around T_{max} with the sparse sampling approach in the included phase III outpatient studies. The high ETA-shrinkage for V/F could be a potential limitation of the current simulation approach to predict C_{max}, and assess C_{max} ratio between pediatric and adult populations. The ETA-shrinkage for k_a under fed condition was also high (89.6%), but this was likely due to only 200 pregabalin readings from 11 patients in study

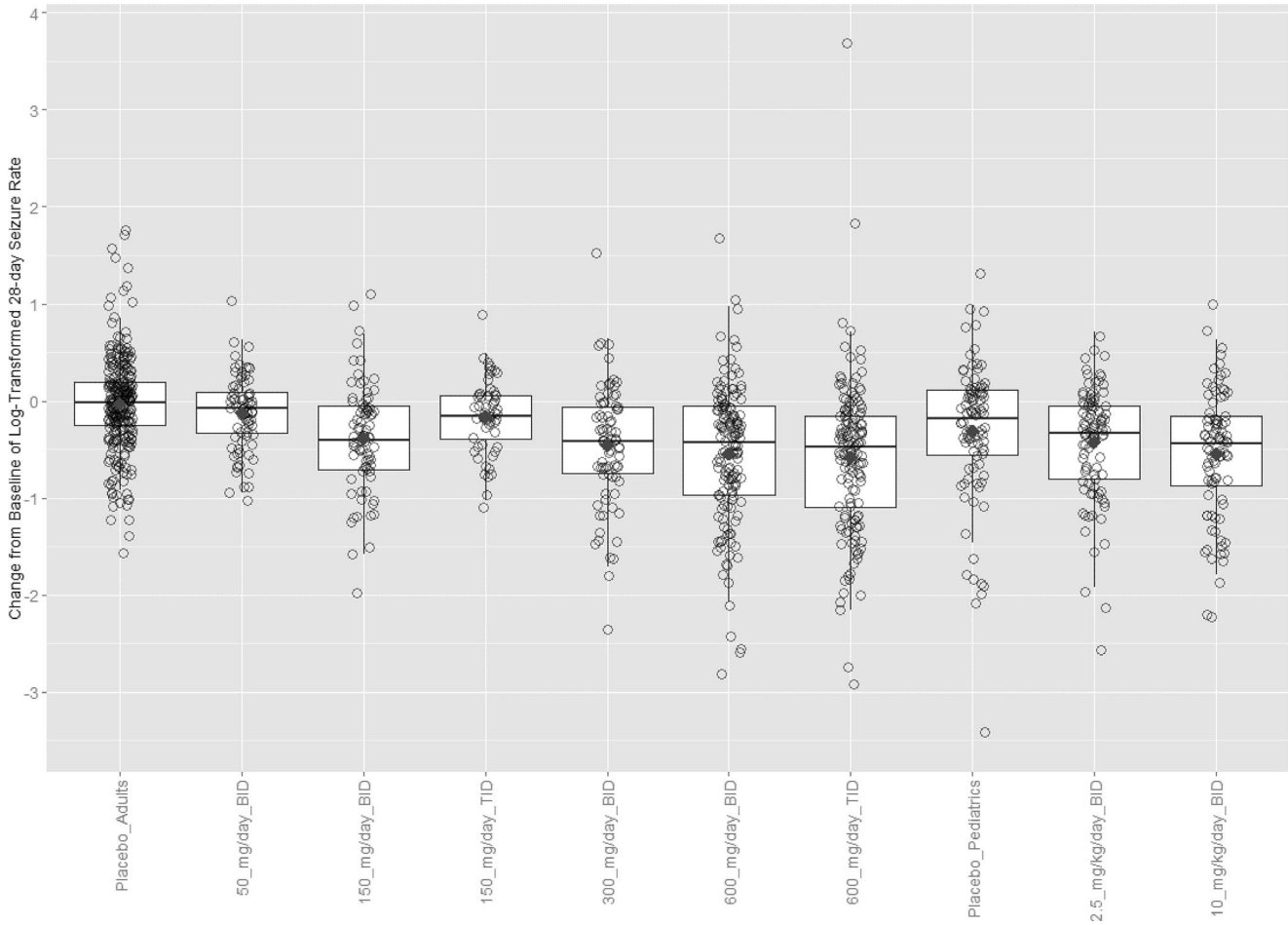

Figure 2 Distribution of change from baseline of log-transformed 28-day seizure rate (all partial onset seizures) by population and treatment. Circles represent the individual observations. Boxes indicate the interquartile range with the median of the individual treatment group shown by a horizontal line. Grey diamonds represent the group means. Whisker lines represent 1.5 times the interquartile range below the first quartile or above the third quartile. For pediatric study A0081041,[4] 2.5 mg/kg/day included 2.5 mg/kg/day in patients ≥ 30 kg or 3.5 mg/kg/day in patients < 30 kg, with maximum 150 mg/day; 10 mg/kg/day included 10 mg/kg/day in patients ≥ 30 kg or 14 mg/kg/day in patients < 30 kg, with maximum 600 mg/day.

1008–003,[18] with known fed conditions, and was not used in the simulations. In contrast, the ETA-shrinkages for k_a under fasted and unknown food status, as well as for CL/F, were lower (46.2% and 27.4%, respectively), consistent with more data being available to support the parameter estimates.

Population dose-response models using a Poisson model[26] or a negative binominal distribution[27,28] with factors of dose or exposure, absence or presence of seizures on preceding day, placebo effect, and the use of mixture model to separate out patients who respond (responders) or do not respond (nonresponders) to treatment, have been used to describe longitudinal daily seizure count data. However, this type of analysis requires intensive computing time given the amount of data and highly variable day-to-day seizure count over a long trial period. We utilized an E-R analysis for a simpler approach,[29] with regression analysis on the seizure data during the double-blind treatment period (LSR28) and factors of

Table 3 Final E-R model parameters for pregabalin in adults and children (aged 4–16 years)

	Baseline effect		Placebo response[a]	Treatment effect	
Data	Intercept	$Slope_{baseline}$		E_{max}	EC_{50}, μg/mL
Adult (A)[b]	0.099 ± 0.066	0.948 ± 0.022	2.37	–1.06 ± 0.363	5.93 ± 3.49
Children (C) + Adult (A)	C: –0.409 ± 0.106	C: 1.03 ± 0.026	C: 2.68	–0.924 ± 0.214	4.69 ± 2.17
	A: 0.110 ± 0.066	A: 0.945 ± 0.022	A: 2.38		

Values are estimate and standard error.
EC_{50}, half maximal effective concentration; E_{max}, maximum response achievable; E-R, exposure-response.
[a]Computed as intercept + $slope_{baseline}$·$baseline_{median}$, for patients with median log-transformed 28-day seizure rate of 3.00 for children or 2.40 for adults. [b]Included 8 patients aged 13–16 years in 1 adult study (protocol 1008-034).

Table 4 Median ratio (children vs. adults) for pregabalin PK exposure based on simulations using bootstrapped data

		Adults (≥ 17 years)		Children (4–16 years)		
		(*n* = 1,000) Median (μg/mL)		All (*n* = 1,000)	< 30 kg[a] (*n* = 391)	≥ 30 kg[b] (*n* = 609)
Parameter	Frequency	150 mg/day	600 mg/day	Ratio to adults		
$C_{av,ss}$[c]	b.i.d.	1.34	5.37	0.91	0.89	0.92
	t.i.d.	1.34	5.35	0.90	0.88	0.91
$C_{max,ss}$	b.i.d.	2.43	9.73	1.01	1.05	0.99
	t.i.d.	1.97	7.86	0.99	1.02	0.97
$C_{min,ss}$[d]	b.i.d.	0.60	2.39	0.75	0.68	0.80
	t.i.d.	0.81	3.23	0.78	0.72	0.81

$C_{av,ss}$, average steady-state concentration; $C_{max,ss}$, maximum steady-state concentration; $C_{min,ss,}$ minimum steady-state concentration; PK, pharmacokinetics. [a]3.5 mg/kg/day (max 150 mg/day) or 14 mg/kg/day (max 600 mg/day) for the equivalent adult doses of 150 and 600 mg/day, respectively. [b]2.5 mg/kg/day (max 150 mg/day) or 10 mg/kg/day (max 600 mg/day) for the equivalent adult doses of 150 and 600 mg/day, respectively. [c]Ratios to adults are the same as areas under the concentration–time curve. [d]$C_{min,ss}$ represents the trough value at 12 hours for b.i.d. dosing and 8 hours for t.i.d. dosing.

the individual's baseline LSR28 and placebo effect. Although this simpler approach does not allow prediction of individual patterns in seizure frequency over time,[29] it is considered adequate for the broad comparison of the dose-response or E-R relationship across patient populations.

The present study also demonstrates that the E-R relationship for pregabalin in patients with FOS was similar in pediatric (4–16 years) and adult patients, after accounting for differences in baseline LSR28 and placebo effect. It should be noted that the adult and pediatric studies were conducted ~ 20-years apart, where differences in clinical practice and management may have contributed to placebo response differences. This is considered in light of data suggesting an increasing placebo effect on efficacy with ongoing AED treatment, and a decreasing placebo-adjusted drug effect of AEDs over the past 2 decades.[30] More specifically, Rheims *et al*., in 2011, demonstrated that responder rates were significantly higher in more recent studies than in older studies.[30] For pediatric patients 4–16 years, anatomic and clinical features of FOS are similar to adults, as are responses to AEDs[31–33] and E-R relationships.[29] Our analyses utilizing pregabalin data are consistent with these conclusions, and provide further validation of E-R relationship similarity in adult and pediatric FOS populations.

Considering the difficulty in recruiting pediatric patients with FOS, only the b.i.d. regimen was investigated in PERIWINKLE. Pregabalin 10 mg/kg/day (including 14 mg/kg/day in children < 30 kg) demonstrated significant reduction in seizure frequency, whereas pregabalin 2.5 mg/kg/day (including 3.5 mg/kg/day in children < 30 kg) showed a numerical decrease in seizure frequency but not of statistical significance.[4] As the sparse pregabalin concentrations and the population PK modeling confirmed pregabalin exposure, the lack of statistical difference at the lower dose in PERIWINKLE could be due to a larger placebo response, hence the smaller placebo-adjusted efficacy vs. adult studies.[2] After taking into account the different placebo responses in the joint analysis, pregabalin demonstrated a similar E-R relationship in adult and pediatric (4–16 years) patients with FOS, consistent with the analysis that supported the full efficacy extrapolation from adults with FOS to this age group.[29] Considering the FDA's advice notice and the totality of the pregabalin data, pregabalin dosage recommendations in the prescription label[2,3] were based on full efficacy extrapolation by matching pregabalin exposures at the approved adult doses, and the safety and tolerability observed in the pregabalin pediatric studies. Safety data cannot generally be extrapolated from adults to children, and still requires specific clinical study.[12] Both b.i.d. and t.i.d. regimens were simulated for the pediatric patients as they had been approved for adult patients. Our simulations and dose predictions collectively supported the pregabalin b.i.d. and t.i.d. dosage recommendations for pediatric patients aged 4–16 years, which were subsequently approved by the FDA as reflected in the pregabalin prescription label.[2]

Future perspectives

There are many challenges in pediatric drug development, particularly in recruitment and PK sampling of vulnerable populations, which may delay the completion of necessary studies to support approval for pediatric use.[34] Model-informed drug development, including the use of extrapolation to replace or reduce the number of required clinical trials in pediatric populations, would help speed up pediatric drug development, and thus deliver medicines to pediatric patients faster.[35,36] Had the extrapolation approach been used for the pregabalin FOS pediatric program, regulatory approval could have been obtained up to a decade earlier. The full efficacy extrapolation in FOS will greatly facilitate more efficient future pediatric drug development in FOS, by reducing the need for phase III studies. There are still significant needs in many other disease areas using extrapolation in place of clinical trials to minimize potential delays and provide effective therapy to pediatric patients. As exemplified in the FOS example, the extrapolation evaluation will require multidisciplinary collaborations, especially modeling and simulations to address questions on similarities in disease, PK exposure, and E-R relationship between adult and pediatric patients.[32,37] This may require the incorporation of more innovative and quantitative approaches to improve the robustness of the analysis.[38,39]

In addition to efficacy extrapolation, we would also like to advocate for pediatric PK extrapolation to potentially replace or minimize pediatric phase I studies, an area which has been gaining credence

since 2015.[18,40] The issues can be highlighted by our earlier trials, such as the phase I pediatric study investigating pregabalin, which took ~ 5 years to complete, and more specifically, the 1 month to < 2 years age group, for which it took > 2 years to recruit sufficient patients. We have demonstrated that a retrospective analysis using population PK analysis[18] and physiologically-based PK modeling confirmed that the pediatric PK of pregabalin, a renally eliminated drug, could be confidently predicted using adult PK observations.[41] Merging pediatric with adult data had minimal impact on adult PK and E-R parameter estimates. For future studies of drugs that are primarily eliminated via renal excretion, or for compounds with well-defined PK properties and high confidence in pediatric PK prediction, we suggest that pediatric PK may be collected using sparse sampling in long-term safety studies, rather than a dedicated pediatric phase I study, to increase the speed of pediatric drug development, allowing earlier access to novel treatments for pediatric patients.

CONCLUSION

We observed similar exposure and E-R relationships in adults and children (4–16 years) treated with pregabalin for FOS. This is consistent with data from clinical trials evaluating other AEDs after accounting for differences in baseline seizure rate and placebo effect. Our modeling and simulation approach used extrapolation to inform and support the dosage guidance provided in the pregabalin prescribing label for pediatric patients. Specifically, the prescribing label states for pediatric patients weighing ≥ 30 kg, dosing should be initiated at 2.5 mg/kg/day (maximum 150 mg/day) divided as two or three doses (b.i.d. or t.i.d., respectively), based on individual response and tolerability. The dose may be increased weekly up to a maximum of 10 mg/kg/day (maximum 600 mg/day). For pediatric patients < 17 years and weighing < 30 kg, dosing should be initiated at 3.5 mg/kg/day (maximum 150 mg/day) b.i.d. or t.i.d. The dosage may be increased approximately weekly up to a maximum of 14 mg/kg/day (maximum 600 mg/day) based on individual response and tolerability.[2] Our observations are further supported by evidence from adequate and well-controlled studies in adults with FOS and PK data from adult and pediatric patients. Our combined modeling approach may provide guidance for future extrapolation assessment from adult to pediatric patients.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

P.L.S.C., S.F.M., L.M., and J.L. are full-time employees of Pfizer and all own Pfizer stock.

AUTHOR CONTRIBUTIONS

P.L.S.C., S.F.M., L.M., and J.L. wrote the manuscript. J.L. designed the research. J.L. performed the research. P.L.S.C., S.F.M., L.M., and J.L. analyzed the data.

DATA AVAILABILITY STATEMENT

Upon request, and participant to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: (1) for indications that have been approved in the United States and/or European Union; or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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